secondary enhancers lie tens of kilobases away. The authors used transgenic flies to show that both nearby and more distant clusters of binding sites drive similar patterns of reporter gene expression for two genes, *brk* and *sog*.

The evolutionary role of these "shadow enhancers" is unclear. One possibility suggested by Hong *et al.* is that they provide an opportunity for natural selection to tinker with regulatory sequences, while the primary enhancers maintain essential gene function. Consistent with this hypothesis, the sequences of "shadow enhancers" evolve more rapidly than those of primary enhancers, which suggests that they operate under fewer functional constraints. The intriguing possibility that "shadow enhancers" more commonly confer expression differences among species could be tested with the type of comparative experimental approach that Prabhakar and colleagues applied to *HACNS1*.

Although identifying functional changes in regulatory sequences remains a serious challenge, these two papers demonstrate the power of combining bioinformatics and experimental tests. However, most regulatory elements are neither highly conserved among species nor composed of clusters of the same binding motif. Indeed, few of the well-documented cases connecting noncoding mutations to trait evolution in humans and flies (*7–9*) involve regions that would have been identified as functional on the basis of sequence conservation or motif clustering.

The challenge now is to develop methods that can recognize functional changes within a much greater proportion of regulatory elements. As phylogenetic sampling of sequenced genomes grows denser, it is becoming possible to carry out unbiased surveys of regulatory change based on genome-scale functional assays (*10*), quantitative genetics (*11*), and tests for positive selection (*12*).

Decades after Jacob and Monod first speculated about the evolutionary importance of regulatory mutations, we are in a position to begin testing their ideas in earnest.

References
1. F. Jacob, J. Monod, *J. Mol. Biol.* **3**, 318 (1961).
2. M. C. King, A. C. Wilson, *Science* **188**, 107 (1975).
3. S. Prabhakar *et al.*, *Science* **321**, 1346 (2008).
4. J.-W. Hong, D. A. Hendrix, M. S. Levine, *Science* **321**, 1314 (2008).
5. S. Prabhakar, J. P. Noonan, S. Pääbo, E. M. Rubin, *Science* **314**, 786 (2006).
6. M. Markstein, P. Markstein, V. Markstein, M. S. Levine, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 763 (2002).
7. N. Gompel, B. Prud'homme, P. J. Wittkopp, V. Kassner, S. B. Carroll, *Nature* **433**, 481 (2005).
8. N. S. Enattah *et al.*, *Nat. Genet.* **30**, 233 (2002).
9. M. T. Hamblin, A. Di Rienzo, *Am. J. Hum. Genet.* **66**, 1669 (2000).
10. A. P. Boyle *et al.*, *Cell* **132**, 311 (2008).
11. E. E. Schadt *et al.*, *Nature* **422**, 297 (2003).
12. R. Haygood, O. Fedrigo, B. Hanson, K. D. Yokoyama, G. A. Wray, *Nat. Genet.* **39**, 1140 (2007).

ASTRONOMY

The Universe Measured with a Comb

A technique for wavelength calibration promises to revolutionize observational astrophysics, in areas including planet searches and cosmology.

Sebastian Lopez

In 1962, Allan Sandage predicted that an expanding universe should cause a drift in the redshift of cosmological objects, but noted: "With present optical techniques there is apparently no hope of detecting such small changes in redshifts for time intervals smaller than 10^7 years" (*1*). Future extremely large telescopes (with diameters of 30 to 40 m), equipped with powerful spectrometers, could in principle enable such a measurement. However, measuring a systematic change in radial velocity of only 1 cm s^{-1} per year over the course of about 20 years—a measurement referred to as the Sandage-Loeb experiment (*2–4*)—would still be impossible if it were not for the recent development of a new and exquisite wavelength calibration technique called "laser frequency combs" (*5*). On page 1335 of this issue, Steinmetz *et al.* apply this technique for the first time to an astrophysical experiment (*6*), and the results look promising.

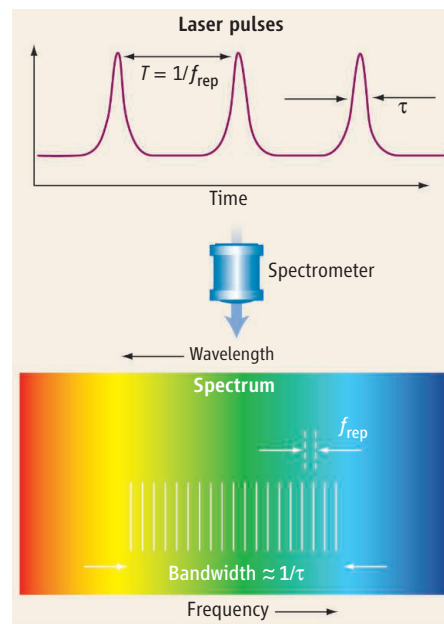The Doppler effect provides astronomers with a precise method to measure radial velocities of stars and galaxies using the observed shift in wavelength (or frequency) of their spectral features relative to laboratories on Earth: The higher the radial velocity, the stronger the effect. And when the light entering the spectrometer comes from distant objects like galaxies or quasars—thus crossing cosmological distances to reach the telescope—their spectra provide information about the geometry and history of the universe as a whole.

Because the universe expands, distant objects can always be assigned with a redshift, a quantity that cosmologists relate to distance and time by fitting various parameters to cosmological models. The past decade has seen a series of breakthroughs in cosmology. The Wilkinson Microwave Anisotropy Probe (WMAP) mission delivered images of the cosmic microwave background that support a

The basics of a laser frequency comb. A mode-locked laser creates femtosecond pulses at gigahertz frequencies, f_{rep} (**top**), that are synchronized with an atomic clock. A spectrum of the pulses (**bottom**) is composed of many modes that are uniformly spaced in wavelength (or frequency) and cover a spectral bandwidth given roughly by the inverse of the pulse duration. Each mode's wavelength (or frequency) does not have to be measured, but instead is given by a mathematical relation that includes f_{rep}, known a priori with very high accuracy. Laser frequency combs could therefore become the perfect wavelength calibration technique for astrophysical experiments that require high accuracy and long-term stability.

Departamento de Astronomía, Universidad de Chile, Casilla 36-D, Santiago, Chile. E-mail: slopez@das.uchile.cl

flat universe, and studies measuring distances to Type Ia supernovae or the large-scale distribution of galaxies, among others, have established that the universe not only expands, but that the expansion is accelerating—presumably due to the effect of an unknown component in the mass-energy budget of the universe called "dark energy." Many projects aim to elucidate what dark energy really is, but all of them rely on a given cosmological model; only the Sandage-Loeb experiment could track the history of the expansion directly, without any previous assumption on the geometry of the universe.

What has been the impediment to fully exploiting present instrument capabilities? Traditional spectral calibration techniques use a crowd of emission or absorption lines at known laboratory wavelengths as reference to map the detector pixels into wavelengths. However, calibration units are subject to uncertainties that unavoidably degrade the wavelength solution: Lines are not evenly distributed in the spectral range of interest, have a wide range of intensities, and sometimes appear blended. These systematic effects become the perennial stumbling block for precision spectroscopy. They limit the capabilities of current high-resolution spectrometers and hinder experiment repeatability, crucial for any long-term monitoring.

The recently developed laser frequency combs (3, 6–9) may offer the solution. Such a comb is the spectrum of a femtosecond "mode-locked" laser that delivers pulses at repetition rates f_{rep} of ~1 GHz (determined by the round-trip time in the laser cavity). When these pulses pass through a spectrometer, a regular train of modes is produced in the frequency domain, each of them evenly separated by f_{rep} (see the figure) and spanning a spectral bandwidth given by the inverse of the pulse duration. Because time—and thus frequency—is the most accurately measured quantity in physics thanks to atomic clocks, each mode's frequency (or wavelength) is accurately known a priori and can be used as a perfect ruler to calibrate astronomical spectra.

Steinmetz et al. now report the first astronomical spectrum (of the Sun) calibrated with a laser frequency comb. Besides slightly outperforming current best standards of accuracy using just a small bandwidth, the team was also able to characterize the stability of the instrument in an unprecedented fashion. Use of larger bandwidths should allow wavelengths to be measured with a stable precision of 1 part in 10 billion, opening a new era in astronomical spectroscopy.

Full implementation of laser frequency combs in large telescopes will require cover-

age of the entire optical range. Once this challenge is overcome, at least two other astrophysical experiments besides the future Sandage-Loeb test should benefit from the use of this technique.

First, some astronomers have wondered whether the atomic physics responsible for the redshifted absorption lines seen in the spectra of distant quasars has remained the same over cosmological times. The values of fundamental constants or combinations of constants—like the proton-to-electron mass ratio or the fine-structure constant—determine the relative positions of the lines in the quasar spectra. Thus, one could in principle compare the value of those constants then ("at high redshift") and now (on Earth) to determine whether they have remained constant. By choosing particular methods and sets of lines, different groups have arrived at diverging conclusions. After a decade of research, the debate is now centered on the systematic effects inherent to the observations. Laser frequency combs could help to identify the origin of these systematic effects.

Second, the precision and stability offered by laser frequency combs could greatly help

astronomers looking for exoplanets (which orbit stars other than the Sun). Such planets imprint small changes on the radial velocity of their solar system, and monitoring the radial velocities of bright stars has thus become the most reliable way of finding planets. However, the smaller the planet, the smaller the drift in radial velocity. Discovering Earth-like planets orbiting solar-like stars in the "habitable zone" (where life could exist) requires a precision of about 5 cm s^{-1} and a stability of about 1 year. This should be an easy task for this new technique.

References and Notes
1. A. Sandage, *Astrophys. J.* **136**, 319 (1962).
2. A. Loeb, *Astrophys. J.* **499**, L111 (1998).
3. M. T. Murphy *et al.*, *Mon. Not. R. Astron. Soc.* **380**, 839 (2007).
4. J. Liske *et al.*, *Mon. Not. R. Astron. Soc.* **386**, 1192 (2008).
5. T. W. Hänsch and J. L. Hall received the 2005 Nobel Prize in Physics "for their contributions to the development of laser-based precision spectroscopy, including the optical frequency comb technique."
6. T. Steinmetz *et al.*, *Science* **321**, 1335 (2008).
7. Th. Udem, R. Woltzwarth, T. W. Hänsch, *Nature* **416**, 233 (2002).
8. C. Araujo-Hauck *et al.*, *Messenger* **129**, 24 (2007).
9. C.-H Li *et al.*, *Nature* **452**, 610 (2008).

MEDICINE

The Cart Before the Horse

Janet D. Rowley[1] and Thomas Blumenthal[2]

Chimeric RNAs, transcribed from malignancy-associated chromosomal translocations, can also arise from RNA trans-splicing in normal cells.

Since the identification of specific regions in human chromosomes that undergo recurring structural rearrangements (translocations) and cloning of the associated breakpoint genes, the fusion of genes has been viewed as a unique event in abnormally growing, usually malignant, cells (1, 2). However, the study by Li *et al.* on page 1357 in this issue (3) indicates quite the contrary, turning at least one paradigm of cancer cytogenetics on its head.

Li *et al.* report that in normal human endometrial tissue, there is a low amount of a messenger RNA (mRNA) that corresponds to sequences from two genes, *JAZF1* on chro-

mosome band 7p15 and *JJAZ1/SUZ12* on chromosome band 17q21. Moreover, this chimeric mRNA is identical to that seen in 50% of human endometrial stromal sarcomas, in which there is a 7;17 chromosomal translocation that results in a gene fusion, even though no translocation is detected in normal endometrial cells. The product encoded by the chimeric mRNA is a fusion protein that is expressed in cultured cells, and consequently, could confer cellular resistance to programmed cell death and increased growth (under conditions where expression of the endogenous *JJAZ1* gene was suppressed). Further, this fusion mRNA is expressed in a cyclical manner in normal endometrial cells, most readily detected at the beginning and end of the menstrual cycle when concentrations of estrogen and progesterone are low.

How is this fusion mRNA made in the absence of a corresponding gene fusion?

[1]Department of Medicine, University of Chicago, 5841 South Maryland Avenue, MC 2115, Chicago, IL 60637, USA. E-mail: jrowley@medicine.bsd.uchicago.edu [2]Department of Molecular, Cellular and Developmental Biology, University of Colorado, Boulder, CO 80309, USA. E-mail: tom.blumenthal@colorado.edu